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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,693	01/29/2002	Andrew Shiau	UCAL-256/01US	9894

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EXAMINER	
NASHED, NASHAAT T	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 08/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,693	SHIAU ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-154* is/are pending in the application.

4a) Of the above claim(s) *1-43,49,51-135,140 and 141* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-48,50,136-139 and 142-154* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/20/05 & 1/20/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The application has been amended as requested in the communication filed March 9, 2005. Accordingly, claims 137, 142, 144, and 148 have been amended and claims 149-154 have been entered.

In view of the decision on the petition filed March 9, 2005, elected Group V (44-48, 136-138, and 142-148) and VII (claim 139) are rejoined.

Claims 44-48, 50, 136-139, and 142-154 are under consideration.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. In particular, the application fails to comply with 37 CFR 1.821 (d), which states:

> "Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application."

The non-compliance are found through out the specification, see for example the figure description, page 10, line 26, page 11, line 31, page 13, and page 19, in particular, example 1 at page 35 line 3 and 4; and claims 46, 48, 137, 138, 142, and 143. It should be noted that the results in appendixes 1 and 2 represents a disclosure of one or more polypeptide sequence. If the amino acid sequence representing the results in the appendixes is part of the sequence listing, the heading of the Tables should identify the polypeptide(s) by sequence identification number. If the sequence is not in the sequence listing, applicants must file a new paper copy of the sequence listing contain the sequences in the Tables, and a Computer Readable Form of the sequence listing (CRF) accompanied with a statement indicating that the paper copy of the sequence listing and CRF are identical and that they contain no new matter.

In response to the above, applicant has made an effort to perfect his compliance with the sequence rule. Applicant, however, has failed to perfect his compliance with the sequence rules after entering both amendment filed 1/29/03 and 3/9/05. All amino acid residues describe the three dimension structure in the specification should be accompanied by a sequence identification number at <u>each occurrence</u>. The amendment to page 49 fails to overcome the objection with regard to Appendix I and II.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and

use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44-48, 50, 136-139, and 142-153 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons set forth in the prior Office action mailed December 9, 2004.

In response to the above rejection, applicants argue that the claimed invention is fully described in the specification.

Applicants' arguments filed March 9, 2005 have been fully considered, but they are found unpersuasive. As indicated in the prior Office action, claims 44-48, 50, and 142-147 as well as new claims 149-151 are directed to all possible crystals of a complex of a portion of an estrogen receptor ligand binding domain, an agonist, and a molecule bound to a co-activator-binding site of said estrogen receptor. While the specification teaches various proteins to be crystallized, agonist and antagonist, the specification does not provide any correlation between the primary structure of a protein and the crystallization conditions to be used in crystallizing the various proteins and their complexes. It is well established in the art that even a single amino acid substitution would render a protein crystallizable or not under specific crystallization conditions. The specification clearly describes the crystallization of the same protein with one agonist and one antagonist at page 36, where the different complexes crystallized under different crystallization conditions in two different unrelated space groups. No other crystal or crystallization conditions are described. As indicated in the previous Office action, claims 136-139 and 148, as well as new claims 152-154, they are directed to all possible purified and isolated composition comprising an estrogen receptor ligand binding domain from any biological source, any agonist bound to the ligand binding domain and any co-activator bound to the activator binding site in solution, vapor, amorphous precipitate, or crystalline form. Since the claims read on any crystal, the discussion in the previous paragraph is applicable to these claims.

Claims 44-48, 50, 136-139, and 142-154 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response to the above rejection, applicants argue that the specification fully enable the claimed invention.

Applicants' arguments filed March 9, 2005 have been fully considered, but they are found unpersuasive. Enablement requires a disclosure sufficient to allow a person

of skill in the art to practice the full scope of the claimed invention without undue experimentation. The previous Office action sets out a *prima facie* case of non-enablement, explaining by sound scientific reasoning why a person of ordinary skill in the art would doubt that the guidance of the specification would enable practice of the full scope of the claimed invention without undue experimentation. Applicants have presented no evidence or, indeed, any arguments to establish the adequacy of the disclosure to enable the scope of the instant claims. Applicants merely assert that the teaching of the specification would allow one of ordinary skill in the art to obtain any crystal of a ternary complex containing any estrogen receptor-binding domain, any ligand including the wish list in new claims 149 and 152, and any co-activator in any space group. It should be noted that the specification does not specify which protein was used for crystallization. In the previous Office action, the examiner made unsupported assumption about the protein that had been crystallized, i.e., Met-Asp-Pro fused to the N-terminus of the ligand-binding domain of residue 297-554 containing 361 amino acid residues. Appendix I contain atomic coordinates for 345 residues and no mentioning of the missing residue in the application to be found. The 244 amino acid residues polypeptide of SEQ ID NO: 27 contains a deletion mutation, when compared to the wild-type human binding domain. Similarly, SEQ ID NO: 28 appears to be identical to SEQ ID NO: 27 except that 9 undefined amino acid residues are inserted following Phe-157. Clearly, the specification is confusing and evasive with regard to the exact amino acid sequence, which has been crystallized. Applicants make no effort to explain why they consider the disclosure of a single crystal ternary complex wherein the binding domain amino acid sequence is undefined is sufficient enablement for any crystal to any ternary complex of any binding domain having any amino acid sequence, any activator, and any ligand. Conclusory statements unsupported by evidence or scientific reasoning are insufficient to overcome the *prima facie* case of non-enablement set out in the previous Office action.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 44-48, 50, 138, 142-147, 149, and 152 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for these rejections:

(a) The phrases "a portion of an estrogen receptor binding domain" in claims 44 renders the claim indefinite. For examination purposes only, the phrase "a portion of an estrogen receptor" is assumed to mean any protein or polypeptide that bind estrogen from any biological source including both the a- and b-receptors. The word portion does not identify which portion the applicants are referring to, and the word domain does

not identify a specific portion of a protein. For examination purposes only, the phrases in combination are assumed to be any fragment containing the ligand-binding site of an estrogen binding protein, which makes the claim indefinite.

Applicants traverse the rejection and refer the examiner to page 12, lines 14-19. Also, they further argue that the word "domain" does not specify a specific portion of a protein and its

Applicants' arguments filed March 9, 2005 have been fully considered, but they are found unpersuasive. The examiner regrets his misreading of the claim, but the claim remains indefinite for the reasons above. At page 12, lines 14-19, the specification defines the phrase "portion thereof" as it relates to atomic coordinates and not to a polypeptide. The atomic coordinates defining a portion of the binding site may be utilized in identifying potential "agonist" *in silico*. The claim, however, is directed to a crystal of a protein in supposedly active conformation capable binding a ligand and an activator.

(b) The phrase "derivative thereof" in claim 48 renders the claim indefinite. The phrase is not defined by the claim or the specification, and one of ordinary skills in the art would not know the metes and bound of the claimed invention.

Applicants traverse the rejection and refer the examiner to page 26, line 24, where a definition of "derivative thereof" can be found.

Applicants' arguments filed March 9, 2005 have been fully considered, but they are found unpersuasive. The phrase "derivative thereof" does not even appear in the entire paragraph.

(c) The abbreviations or acronyms "GRIP1" in claims 138 and 143, and "o,p-DDT" in new claims 149 and 152 are not defined at least once in the claims. It should be noted that the abbreviation "o,p-DDT" is not even defined in the specification at page 19, lines 23-25.

Applicants traverse the rejection and point out that the term is well known in the art and refers to "Glucocorticoid Receptor Interacting Protein 1".

Applicants' arguments filed March 9, 2005 have been fully considered, but they are found unpersuasive. The claim refers to a specific protein with the disclosed amino acid sequence of SEQ ID NO: 4. The insertion of the sequence identification number after GRIP1 would obviate this rejection.

(e) Claims 45-47, 50, and 142-147 are included with these rejections because they are dependent on a rejected claim do not cure its deficiencies.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 136 and 137 are rejected under 35 U.S.C. 102(b) as being anticipated by Heery et al (IDS reference).

Applicants traverse the rejection and argue that Heary *et al.* do not teach a purified complex and therefore, the reference does not anticipate the claims.

Applicants' arguments filed March 9, 2005 have been fully considered, but they are found unpersuasive. Applicants should note that claims 136 and 137 are not limited to the three component cited in claim 136. Claim 136 reads "An isolated and purified protein complex Comprising: .....". The word "comprising" indicates the complex could contain other component such as glass beads. Applicants read the word purified as mean "purified to homogeneity". There is no such a limitation in the claim. As indicated in the previous Office action, the spots on the gels shown Figures 3a and 3b and marked GST-AFT+ correspond to the purified ternary complex consisting of GST-AF2, E2 and SRC1a. Thus, contrary to the applicants' opinion, the reference anticipate the claims.

Allowable Subject Matter:

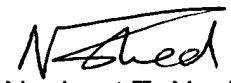
Claims directed to a crystalline composition consisting of a monoclinic crystal in space group $P2_1$ consisting of the ternary complex of the polypeptide corresponding to Met-Asp-Pro fused at the N-terminus of a peptide consisting of residues 297-554 of human estrogen a-receptor identified by a sequence identification number, the agonist diethylstilbestrol, and the polypeptide of SEQ ID NO: 4 would be considered favorably.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen M. Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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Primary Examiner
Art Unit 1656